Remarks

Claims 16 - 31 are pending. Favorable reconsideration is respectfully requested.

The present invention pertains to an improvement in the cleavage of carbamatoorganosilanes to form isocyanatoorganosilanes. The latter are important reactive silanes which have many uses. However, their availability has been limited and what products were available were expensive. Both these factors have linked the products use, and are due to the difficulty of preparing these products on a commercial scale.

The most common route to producing organic isocyanates has been phosgeneration of the corresponding amine followed by thermolysis of the resulting carbamoyl chloride. However, phosgene is very toxic (used as a poison gas during the first World War) and thus non-phosgene methods have been long sought. One method which had promise and may actually be used in commercial production today was the reaction of organic and especially aliphatic amines with urea and alcohol to form the corresponding O-carbamate, followed, after purification, by thermolysis to the isocyanate. Cleavage is disclosed, for example in U.S. Patent 4,530,796 and other patents assigned to BASF AG naming Franz Merger and/or Frederick Towae as inventors. These patents show very clearly the problems associated with thermal cleavage of carbamates: many byproducts, only moderate yields, and reversion of the isocyanate back to the O-carbamate by reaction with the alcohol cleavage product before these products can be separated.

For silyl isocyanates, however, thermal cleavage, despite the many byproducts and low yields, has continued to be one of but few viable processes for manufacturing isocyanatoorganosilanes. Such a method was proposed, for example in U.S. 3,598,852 which issued in 1971. In Example 2, a reasonable yield of product was obtained, but the process required refluxing at 1 mm pressure, and took five hours at 84°C to complete. It is known that while higher temperatures increase the reaction rate, the specificity for the desired product decreases, more starting O-carbamate must be recycled, and more undesirable byproducts are

formed. As the 3,598,852 patent indicates, if too much thermal stress, placed on the starting reactants, *i.e.* by heating too rapidly, significant amounts of isocyanurate byproducts are formed, in particular, the 6-membered cyclic isocyanurates. Thus, the '852 patent directs the skilled artisan to avoid rapid heating.

The present inventors have discovered that if the thermolysis of carbamatoorganosilanes is conducted in the presence of microwave energy, the reaction rate is dramatically accelerated, and the ratio of byproducts to end products is unexpectedly more favorable.

Claims 16 - 31 have been rejected over Kammel U.S. 6,812,361 ("*Kammel*") in view of Greene et al. U.S. 6,084,226 ("*Greene*"). Applicants respectfully traverse this rejection.

Kammel, like U.S. 3,598,852, is directed to preparing isocyanatoorganosilanes by thermal cleavage of silyl carbamates. However, *Kammel* does so in the gas phase by volatilizing the carbamate and thermolyzing at 300 - 600°C in the presence of a heterogeneous catalyst. Following distillation of the crude product mixture, a high purity product is produced (97%), but no information on yield or reaction time is disclosed.

Greene is directed to a multi-stage apparatus in which microwaves are employed for rapid heating of repetitive samples, for example for use in the Kjeldahl analysis for nitrogen, where the power of the microwaves are reduced both by lowering the power level and restricting the duty cycle. *Greene* indicates that the principle advantage of microwaves is that the sample and not the container is heated, thus allowing more rapid processing due to the lesser time required to achieve the desired operating temperature. Contrary to the statement of the Office, *Greene* does not indicate that microwaves increase reaction rate. Rather, by use of a non-absorbant container, "time to temperature" is reduced. *Greene* even cautions in column 2 (lines 45 - 50) that too much microwave power can lead to overheating, resulting in an entirely different reaction than that expected.

The Examiner cites the passage in *Greene* which discloses that the advantages of microwave assisted reaction is the shortening of time for the chemical reaction and direct targeting of heat. However, neither of these is directed to the rate of the reaction, and in general, the art indicates that it is impossible to predict whether any given reaction will be favored by microwaves. In reactions which occur in neat liquids or in organic solvent, the art indicates that the only advantage, if any, is reduced time to temperature, since the ultimate temperature reached is limited by the boiling point of the neat liquid or solvent. Furthermore, there is no established relationship between use of microwaves and product specificity or generation of byproducts.

As indicated by Bernd Ondruschka, Letters, CHEMICAL AND ENGINEERING NEWS, March 28, 2005, (attached) the "optimism" for use of microwave assisted synthesis is not justified, citing recent investigations in Jena, Germany. G. Majetich et al., "The Use of Microwave Heating to Promote Organic Reactions," J. MICROWAVE POWER AND ELECTROMAGNETIC ENERGY, Vol. 30, 1, pp. 28 - 45 (attached) investigated a number of reactions including the irreversible Diels-Alder Reaction, Cope and Claisen Rearrangements, ene reactions, conversion of alcohols to bromides, conversion of organic bromides to iodides, oxidations, and Fischer Esterifications. The results show that microwave synthesis generally reduced reaction time significantly, but did so because the microwave samples were conducted in sealed pressure containers, which allowed the reaction to take place at higher temperature, which is not possible under open reflux conditions. Thus, the duration of the reactions are not directly comparable, and cannot be used to assess reaction rates, since the reactions took place at different temperatures. When corrected for this temperature differential (which was due to use of pressurized containers) by application of the Arrhenius equation, the ratio of reaction rates of all microwave assisted reaction to the thermal reaction varied widely, from only 10% of the reaction rate of the purely thermal reaction to 72 times the rate. In the 45 reactions studied, 22, or about 50%, were slower than the corresponding thermal reactions. There was absolutely no predictability in these results. For example, in the Diels-Alder Reactions (1-5), the relative ratios were 0.91, 6.0, 0.87, 0.54, and 0.10.

Moreover, the yields varied widely as well. In the Diels-Alder Reaction, the ratios of microwave yield to conventional thermal yield were 0.87, 1.26, 0.98, 0.91, and 1.04 - in other

words, in most reactions, a decrease in yield. In the ene reactions, three examples showed increases in yield, with yield ratios ranging from 2.35 to 1.10. In conversion of organic bromides to iodides, in the three examples, there was on average very little effect on yield. In the Fischer esterifications, on average the yields dropped when using microwaves. In aryl ether cleavage, all three reactions studied showed a very slight decrease in yield when microwaved. A study of the 45 examples clearly indicates to one skilled in the art, that provided the reaction can take place in a pressurized environment, reaction times can be considerably shortened due to the increased reaction temperature, but yield is very substrate dependent, and cannot be predicted. If conditions (pressure and temperature) are the same, however, as is the case in neat and solution reactions, even the relative rates are expected to be the same. The article also produces the conclusion that even when the rates are different, the actual reaction rates will only vary from about 0.5 (slower) to 2.0 for the vast majority of reactions.

C. Oliver Kappe et al., MICROWAVES IN ORGANIC AND MEDICINAL CHEMISTRY, Wiley-VCH ©2005 indicates on pages 3 - 4 that for solvent borne reactions, reflux temperature is a limiting factor, and for this reason, high boiling solvents have been used in open vessels, but present "serious challenges to product isolation and recycling of solvent." This reference may be viewed on the web.

Gedye and *Wei* investigated the synthesis of 1,5-diazepin-2-ones by thermal and microwave techniques, and found virtually no difference in rates or yields between the microwave and thermally heated reactions. *Gedye et al.*, CAN. J. CHEM., 1998, 76, 525-532.

It is clear from these references that no prediction can be made relative to temperature-corrected reaction rates or yields. Thermolysis of carbamatoorganosilanes had not been investigated prior to Applicants discoveries, and one skilled in the art simply could not predict whether the use of microwaves would increase or decrease either the reaction rate or yield. At best, one could only expect a slight difference in the overall processing time (but not the reaction rate) due to more rapid heating to temperature. This is not a gas phase reaction where a heterogenous catalyst which absorbs microwaves can be heated to higher temperatures than the surrounding gas, but rather is a liquid phase reaction where the temperature is limited

by the boiling point of the liquid phase, and where a heterogenous catalyst is used, even a microwave absorbing catalyst, heat is rapidly transferred to the liquid phase. Moreover, the cleavage of O-carbamates to isocyanate and alcohol is endothermic, and thus the reverse reaction is accelerated by increased thermal stress, as is also the formation of byproducts, as indicated by U.S. 3,598,852.

In the present application, the inventors have found a surprising and unexpected increase both in reaction rate and yield, and a surprising decrease in byproduct formation. With reference to the latter, for example, six membered isocyanurate formation is virtually completely avoided (specification, page 9). In U.S. 3,598,852, however, those inventors cautioned that increased thermal stress actually increases isocyanurate formation.

In Comparative Example 1, methylcarbamatopropyltrimethoxysilane ("MCPTS") was heated very rapidly (to minimize any effect of "time to temperature") to 225°C with a heterogenous Fe_2O_3 catalyst in a glass vessel with distillation column and overhead condenser. The sample size was also very small, which also reduced the heating time, such that the "time to temperature" was only a small fraction of the total reaction time. Even after 60 minutes at 225°C, no overhead condensate was collected, and analysis of the still residue revealed that 96% of the MCPTS remained unreacted (or had reacted and reverted). Only 0.9% of product, γ-isocyanatopropyltrimethoxysilane ("IPTS") was formed, along with 2.6% byproducts. The ratio of byproduct to product was 2.9, in other words almost 300%!

Example 2 is directly comparable, employing exactly the same amounts of reactant and catalyst. After only 4 minutes, 1.7 ml of condensate from the refluxing mixture was obtained. The condensate contained 16% IPTS and 25% MCPTS, which could be recycled. The still bottoms containing 85% by weight unreacted MCPTS, 12.5% by weight of IPTS, and 2.5% byproducts. The ratio of byproducts to IPTS in the still was only 0.20. When the IPTS in the overhead is included also, the ratio even decreases slightly to about 0.19.

There is no way that the decrease in byproduct formation relative to product yield could have been predicted. The decrease in byproduct amount is dramatic, surprising, and

unexpected. Further surprising and unexpected is that in the comparative example, despite being at decomposition temperature for 60 minutes, no overhead was collected. The industrial preparation of IPTS requires a continuous or semibatch technique. It is clearly impossible industrially to heat (by any means) a commercially sized batch of MCPTS to form only a minuscule amount of product in the reaction vessel, and then isolate that amount by distillation from the remainder. The microwave assisted process not only produces higher yield and less byproduct, with a reaction rate some 75 times higher[1], but is also commercially viable.

Example 1 is not a direct comparison to Comparative Example 1, but is perhaps even more instructive, since no catalyst of any kind is present. Despite the absence of catalyst, this reaction was not only 40 times faster than catalyzed Comparative Example 1, but also showed surprising and unexpected difference in both yield and byproduct/product ratio. Importantly, it should again be noted that in all these reactions, the small reactant amount of 20 ml can be rapidly heated by any method. The time for 20 ml to reach 225°C in a hot oil bath is very short. Even if the microwaved reactions reached this temperature in two or three seconds, the small difference between the time-to-temperature of the thermal versus the microwave heated reactions could only influence the overall time of reaction by a very small percentage, and the increase in yield and decrease in byproduct formation are completely unexplained and cannot be related to the shortened time-to-temperature achieved with microwaves.

The Examiner states that the prior art obtains the same effect on yield and purity of isocyanatoorganosilanes. However, this statement is completely unsupported by the prior art, and is completely at odds with the side-by-side comparative examples in the specification. It is true that *Kammel* reports that product purity can reach >97% after distillation, which is also the case with the present invention (see Specification, page 9). However, this refers to a down stream distillation of the crude product overhead condensate. *Kammel* does discuss that in his very different process gas phase reaction over heterogenous catalyst), cyclic isocyanurate formation is also minimized. However, the *Kammel* process is not comparable to the present

[1]Unlike comparing reactions in open v. closed pressurized vessels, Comparative Example 1 and Example 2 are directly comparable, since their maximum temperature is limited by the boiling point of the neat reactants.

process. Modifying the *Kammel* process to a liquid phase process, results in the procedure used in Comparative Example 1, a liquid phase process with heterogenous catalyst. Yet in this process, the amount of byproducts formed is almost 300% of the product formed. *Kammel* also does not discuss the yield. Thus, the prior art does not disclose similar yields, etc., and Applicants by their direct comparison , show the surprising and unexpected benefits of the claimed process.

For all of the reasons expressed above, Applicants submit that the rejection over *Kammel* and *Greene* cannot stand. If the Office is to maintain the rejection, the Office must point to a reference which teaches or suggests that an increase in reaction rate, an increase in yield, and a decrease in byproduct formation would be expected for the thermolysis of carbamatoorganosilanes. The prior art clearly shows that there is no predictability with respect to different classes of reactions, and thus a generality that by use of microwaves the rate, yield, and freedom from byproducts can be improved is at most conclusory and cannot be used to support a rejection. *See, e.g. In re Soli*, 137 USPQ 797 (CCPA 1963); *In re Wagner*, 152 USPQ 552 (CCPA 1967).

The dependent claims do not represent, as the Office states, mere optimization which "are deemed to be obvious." Furthermore, such "blanket" rejections are contrary to both law and Patent Office policy. Each claim should be reviewed for compliance with every requirement of patentability. Each claim limitation must be disclosed, taught, or suggested by the prior art. *See, e.g.* MPEP § 2106 II.

With regard to claim 22, for example, none of the art teaches or suggests these catalysts. How can they therefore be obvious? How could they be "optimizations"? Claim 20 requires a homogenous catalyst. The Examiner states that it would be obvious to optimize the catalyst used. However, the reference cited by the Examiner, *Kammel*, is specifically directed to heterogenous catalysts. *Kammel* requires these, and it would certainly be far from obvious to replace the very gist of his invention with something totally opposite. Moreover, *Kammel* is a gas phase reaction over the heterogenous catalyst. A homogenous catalyst could not possibly work in his process. *Kammel* teaches away from the subject matter of claim 20. Teaching away

is a strong indication of non-obviousness. *W.L. Gore v. Garlock*, 220 USPQ 303 (Fed. Cir. 1983).

Claim 31 requires a gas phase reactor located downstream from the microwave reaction chamber. No reference teaches or suggests this combination. If the rejections of the dependent claims are to be maintained, a reference which teaches all the dependent claim limitations which is properly combinable with the other references must be supplied. Withdrawal of all rejections of record is solicited.

Applicants submit that the claims are now in condition for Allowance, and respectfully request a Notice to that effect. If the Examiner believes that further discussion will advance the prosecution of the Application, the Examiner is highly encouraged to telephone Applicants' attorney at the number given below.

The fee of $460.00 to cover the Petition fee is being transmitted electronically herewith. Please charge any additional fees or credit any overpayments as a result of the filing of this paper to our Deposit Account No. 02-3978.

Respectfully submitted,

Christoph Ruedinger et al.

By _____
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ACS membership: A real bargain

I WOULD LIKE TO GIVE A PARTIAL RESPONSE to ACS member Gary J. Banuk's letter "Finding a Future for ACS" (C&EN, March 7, page 4).

I believe ACS dues are an understated "bargain" well worth the price of membership, which goes well beyond the two following examples. ACS offers a portfolio of insurance packages and discounts exclusive to the society and at surprisingly low costs. C&EN provides current information on industry happenings, and frequent in-depth reviews identify those centers from which future discoveries and advances in the health sciences will come. For members who are interested in building wealth through investments, C&EN is a treasure of information and easily competitive to investment letters costing far more than ACS dues.

If President George W. Bush has his way with revamping Social Security, joining ACS would be a worthwhile suggestion.

H. I. SILVERMAN
Framingham, Mass.

Microwave cooldown

THE ARTICLE "RIDING THE MICROwave" attempts to convince C&EN readers that microwave-assisted syntheses and processes are on their way to solving important societal problems in the near future (C&EN, Dec. 13, 2004, page 14). The piece does this by quoting selected scientists (such as Nicholas Leadbeater, C. Oliver Kappe, and Jason Tierney); leading manufacturers (such as Biotage, CEM, Milestone, and Parr); and the most recent review (*Angew. Chem. Int. Ed.* **2004**, *43*, 6250).

However, considering recent investigations and reviews by the workgroup from Jena, Germany, who are not quoted in the article, this optimism is not justified (see "Microwave-assisted synthesis—a critical technology overview," *Green Chem.* **2004**, *6*, 128; "Microwave-assisted reaction control: Miniplant-scale microwave apparatus with online analysis," *Chem. Eng. Technol.* **2004**, *76*, 961; and "Microwave-assisted chemical reactions," *Chem. Eng. Technol.* **2003**, *26*, 1207). Moreover, more emphasis should be placed on questions about the qualification of technical microwave systems and the validation of microwave-assisted reactions and processes. These considerations must receive more attention in the otherwise mostly synthetic-oriented microwave community. Scale-up experiments that have been performed so far do not fulfill the two previously mentioned certification criteria.

The exploitation of the advantages of dissipative heating for innovative syntheses and reactive separations now requires a close cooperation among synthetic chemists, chemical engineers, and materials scientists. This is the only way that one of Tierney's remark's—"We are able to do new chemistries that we haven't thought possible"— can become reality in the future.

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The Use of Microwave Heating to Promote Organic Reactions

G. Majetich and R. Hicks

This study documents the usefulness of microwave heating for the preparation of a wide variety of organic compounds using a commercial microwave system equipped with a built-in pressure unit and an external temperature monitoring device. The results of control experiments conducted under conventional heating conditions are also provided for each reaction. Most of the reactions studied showed drastically reduced reaction times compared with conventional heating, due to the higher temperatures attained. These results show that microwave heating is useful for preparative organic chemistry.

Key Words:
Diels-Alder reactions, *ortho*-Claisen rearrangements, ene reactions, Conversion of alcohols into alkyl bromides, Finkelstein reactions, Oxidations, Esterifications, Hydrolyses, Williamson ether syntheses, and Aryl ether cleavages.

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Manuscript received Juy 27, 1994. Accepted for publication November 3, 1994.

As early as 1975, there were reports of increased reaction rates for the acid dissolution of samples heated with microwaves [Abu-Samra et al., 1975]. Shortly thereafter, this technology evolved into microwave heating of chemical reactions in sealed containers. Our early studies [Giguere et al., 1986 and 1987] and those of Gedye and coworkers [Gedye et al., 1986; 1988] showed that microwave-promoted reactions occur with a dramatic decrease in reaction time. In some cases, cleaner reactions with easier workups were observed compared with conventional heating. These findings stimulated the study of microwave heating by ourselves and others, and advances in the field are summarized in several reviews [Abramovitch, 1991; Mingos and Baghurst, 1991; Majetich and Wheless, 1995]. In this article we report the results of a survey of common organic reactions: Diels-Alder reactions, *ortho*-Claisen rearrangements, ene reactions, the conversion of alcohols into alkyl bromides, Finkelstein reactions, oxidations, esterifications, hydrolyses, Williamson ether syntheses, and aryl ether cleavages. Conventional reaction conditions for each of the reactions studied were optimized before making comparisons with the microwave results. Hence, many reactions previously thought to require lengthy heating periods, thereby making them ideal candidates for our study, were shown, after optimization, to either be rapid transformations or not require extensive heating.

Materials and Methods

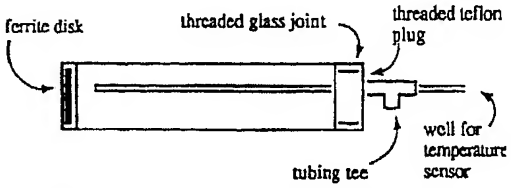
All of the reactions described were carried out using a CEM Model MDS-81D oven equipped with a pressure monitoring device and a MetriCorp fiberoptics temperature monitoring device. The magnetron tube supplies 630 watts (± 70 watts). Effective power levels of 0-100% of this value are available as a train of timed pulses. The MDS-81D unit is designed so that irradiation stops when a predetermined pressure is reached; thus, the pressure monitor functions as a baristat and controls the reaction temperature indirectly. Some changes in temperature were noted in reactions conducted at constant pressure — we attribute these fluctuations to changes in the reaction mixture composition and its volatility.

Most of the experiments were performed in sealed Teflon [poly(tetrafluoro-ethylene)] acid digestion vessels. These Teflon containers can be used at up to fourteen atmospheres of pressure (200 psi). They are resistant to most of the chemi-

cals used in this study; however, at temperatures greater than 250°C, these digestion vessels deform, often with vessel rupture. For microwave-promoted organic reactions in open vessels under atmospheric pressure, see Bose et al. [1990].

The solvents used in our study include dimethylformamide (DMF), water, 2-butanone, methanol, and ethanol — all of which couple efficiently with microwaves. DMF is our solvent of choice for two reasons: first, it is a very efficient coupler of microwaves allowing high reaction temperatures to be reached, and secondly, DMF is miscible with water. Upon completion of the reaction, the DMF is removed by adding water to the reaction mixture followed by standard ethereal workup. On occasion, cosolvents were added to allow the pressure monitoring system to function. For example, in the olefin isomerization (Miscellaneous Reactions), the vapor pressure of dimethyl sulfoxide (DMSO) was too low to engage the pressure monitoring unit; adding ethanol as a cosolvent, which is more volatile than DMSO, overcame this problem without complicating the reaction.

Nonpolar solvents, such as hexanes, carbon tetrachloride, diethyl ether or benzene, do not absorb or couple with microwaves and therefore are generally not useful. In a few cases, the use of nonpolar solvents was unavoidable. In these cases a custom quartz vessel (Figure 1) containing a ferrite disk was employed. Ferrite readily absorbs microwave energy and gives up heat to the reaction mixture through conduction, which provides heat indirectly to the reaction.



The body, including the chamber enclosing the heat source, is of quartz glass. The pressure monitor is connected to the sidearm of the tubing tee. The branch of the tee connected to the vessel is bored to ensure that pressure reaches the sidearm.

FIGURE 1: Custom vessel for heating reaction mixtures that do not couple with microwaves efficiently.

Finally, although effort was made to precisely measure the reaction times, temperatures, and pressures, the experimental conditions reported herein were optimized solely based on reaction yields.

Results and Discussions

Since this journal is interdisciplinary in nature, a brief description has been provided for each class of reaction studied.

Diels-Alder Reactions

Conjugated dienes undergo a cycloaddition reaction with certain multiple bonds to form cyclohexene rings. This process, named the Diels-Alder reaction after its two discoverers, is a powerful synthetic method because two carbon–carbon bonds are formed in a single step to give a functionalized cyclohexene ring. The reaction is most facile when the diene double bonds are electron-rich and the reacting multiple bond of the second component, called the dienophile, is electron-poor. Alkyl groups, aryl groups, and heteroatoms bearing electron pairs are electron-donating and will increase the reactivity of dienes to which they are attached. Atoms bearing either a full or partial positive charge, such as the carbon atom of a carbonyl group, have an electron-withdrawing effect and when directly attached to a dienophile they increase its reactivity.

Diels-Alder reactions involving nonactivated dienophiles typically require heating to temperatures above 300°C. Since the Teflon vessels in the MDS-81D system cannot withstand these temperatures, we selected only Diels-Alder reactions with activated dienophiles for our study. The results are summarized in Table 1.

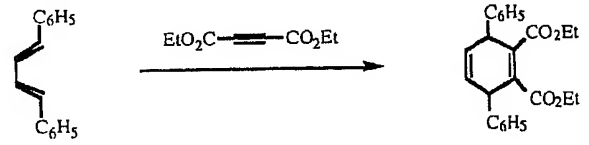
In the first example, the reaction is sluggish due to the steric bulk of the phenyl groups on 1,4-diphenyl-1,3-butadiene even though the dienophile is activated by the electron-withdrawing effects of two esters. The six hour reaction time was reduced by a factor of eighteen under microwave heating conditions, although there was a modest reduction in yield.

In the second example, the absence of steric hindrance in furan makes this reaction more facile than the previous one. The low boiling point of furan (32°C) necessitates that this reaction be done in a sealed vessel to prevent escape of the volatile reactant. This is inconvenient and entails the risk of explosion under conventional conditions. One advantage of the microwave system is the avoidance of these difficulties.

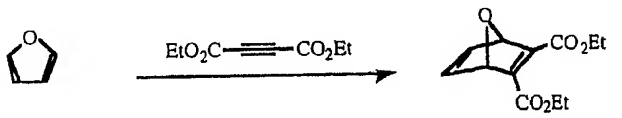
The reactions of anthracene with maleic anhydride (entry 3) and dimethyl fumarate (entry 4) are classic examples of the Diels-Alder reaction. In both cases a dramatic rate enhancement is observed with microwave heating and yields are comparable to those obtained by conventional methods.

Entry 5 shows a hetero-Diels-Alder reaction in which an atom other than carbon is incorporated into the new ring. Although simple ketones do not usually undergo this kind of reaction, the carbonyl group of diethyl oxomalonate is especially electron-poor because of the two ester groups attached to it. Two regioisomers are hypothetically possible from this reaction, but only one product is observed due to steric effects. The rate enhancement under microwave heating in this reaction is modest .

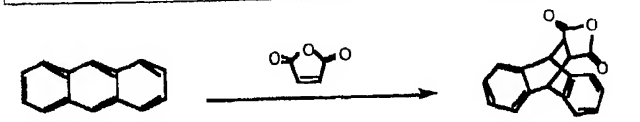
TABLE 1
Diels-Alder Reactions



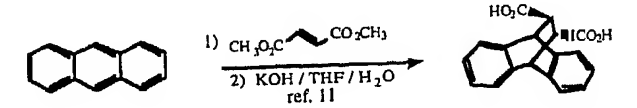
(1)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	198°→194°C (30 psi)
Yield:	67%	58%
Reaction Time:	6 hours	20 minutes



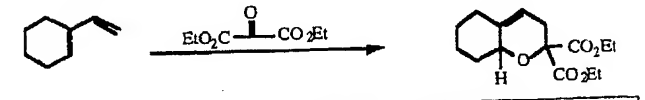
(2)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	175°C(sealed tube)	163°→147°C(30 psi)
Yield:	68%	86%
Reaction Time:	15 minutes	10 minutes



(3)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	190°C (15 psi)
Yield:	86%	84%
Reaction Time:	45 minutes	4 minutes



(4)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	197°→192°C (20 psi)
Yield:	82%	75%
Reaction Time:	120 minutes	12 minutes



(5)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	198°→192°C (23 psi)
Yield:	55%	57%
Reaction Time:	60 minutes	30 minutes

ortho-Claisen Rearrangements

Three important sigmatropic reactions, the Cope rearrangement of a 1,5-diene, the Claisen rearrangement of an allyl vinyl ether, and the *ortho*-Claisen rearrangement of an allyl aryl ether, are depicted in Figure 2. These reactions, along with the Diels-Alder and ene reactions, are examples of pericyclic reactions — processes that involve concerted bond-making and breaking. Cope and Claisen rearrangements are single-step processes. *ortho*-Claisen rearrangements involve the initial pericyclic reaction followed by a tautomerization to restore aromaticity in the product.

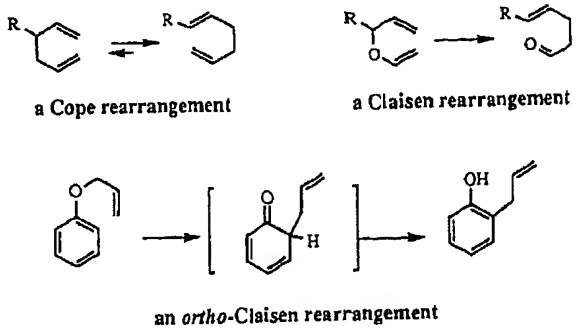


FIGURE 2: *Three Pericyclic Rearrangements.*

The elevated temperatures required (> 190 °C) in the three examples shown in Table 2 were easily achieved using DMF as the solvent. Entry 8 shows a *para*-Claisen rearrangement, in which the allyl unit migrates to the *para* position of the ring through a tandem *ortho*-Claisen / Cope rearrangement process (Figure 3).

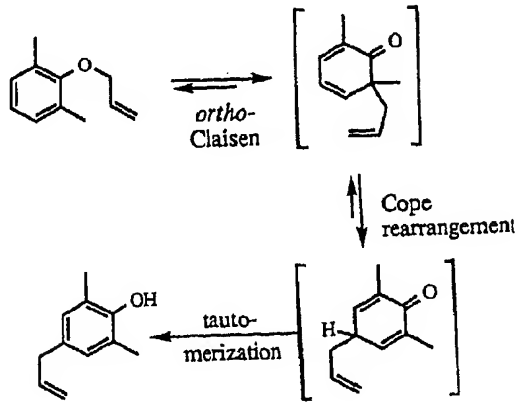


FIGURE 3: *Mechanism of the* para-*Claisen rearrangement.*

Ene Reactions

The "ene reaction" is a reaction of an alkene with an enophile (analogous to the Diels-Alder reaction of a diene with a dienophile) in which a single new carbon — carbon bond is formed and the position of the original double bond shifts through a cyclic transition state.

As in the Diels-Alder reaction, electron-rich enes and electron-poor enophiles are the most reactive. Reactions of enophiles not activated by electron-withdrawing groups usually require temperatures exceeding 300°C, so we selected only those reactions which proceed at temperatures safely attainable in the Teflon vessels. The results are given in Table 3.

Intramolecular reactions are entropically favored over the corresponding intermolecular cases, especially when a five- or six-membered ring is generated. The intramolecular cyclization shown in Entry 9 requires a high temperature because of the unactivated enophile (the triple bond). In contrast, in Entry 10 an activated enophile was employed; even though this reaction requires only twenty minutes under the conventional conditions, a significant rate enhancement is observed using microwave heating.

We also investigated examples of the Alder-Bong reaction [Giguere et al, 1987] which involves an ene reaction followed by an intramolecular Diels-Alder reaction to form interesting polycyclic systems (Figure 4). The intramolecular Diels-Alder step occurs rapidly and thus the intermediate formed by the initial ene reaction is not isolable.

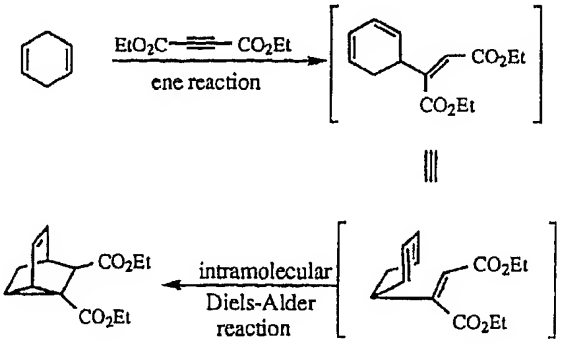
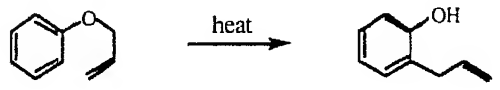
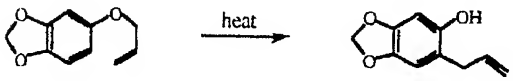


FIGURE 4: Mechanism of the Alder-Bong Reaction.

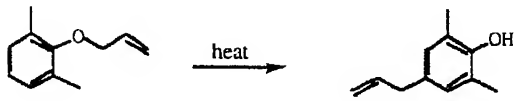
TABLE 2



(6)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	198°→193°C (30 psi)
Yield:	34%	80%
Reaction Time:	80 hours	5 hours



(7)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	195°C (30 psi)
Yield:	72%	97%
Reaction Time:	36 hours	5 minutes



(8)	*Conventional*	*Microwave*
Solvent:	DMF	DMF
Reaction Temperature:	reflux (153°C)	197°→192°C (17 psi)
Yield:	83%	91%
Reaction Time:	4 days	20 minutes

Three examples of the Alder-Bong reaction are reported. In Entry 11, the simplest case, a 120-fold rate enhancement by using microwave heating was observed. Furthermore, decomposition of the reactants, which contributes to the low yield under conventional reflux conditions, was greatly reduced by the shorter reaction time.

The two double bonds of the ene component in Entry 12 are not equivalent, hence two products are possible. The tetrasubstituted double bond is the more electron-rich, and the ene reaction at this bond leads to the formation of the major product 12a. The alternative ene reaction at the disubstituted double bond results in the formation of 12b. The higher yields for this reaction, compared to Entry 11, are attributed to the enhanced reactivity of the ene component which makes the initial ene reaction more favorable than decomposition.

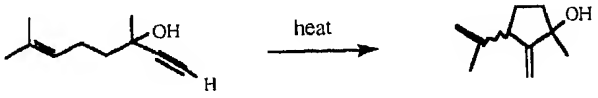
Although two products are also possible in the reaction presented in Entry 13, only one product is formed.

Conversion of Alcohols to Alkyl Bromides

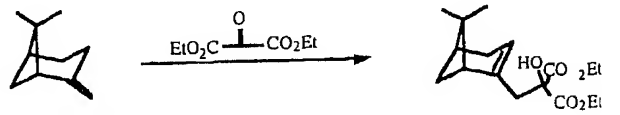
The simplest and most common method for preparing an alkyl halide is to treat an alcohol with a mineral acid. The reaction

TABLE 3

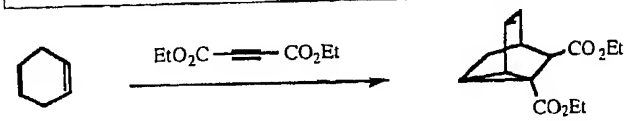
Ene and Alder-Bong Reactions.



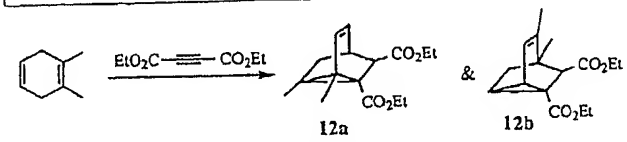
(9) *Conventional*	*Microwave*
Solvent: DMF	DMF
Reaction Temperature: reflux (153°C)	198°→196°C (23 psi)
Yield: 33%	73%
Reaction Time: 4 days	8 hours



(10) *Conventional*	*Microwave*
Solvent: DMF	DMF
Reaction Temperature: reflux (153°C)	199°C (20 psi)
Yield: 68%	71%
Reaction Time: 20 minutes	1 minute

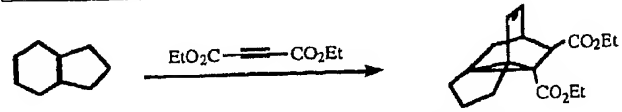


(11) *Conventional*	*Microwave*
Solvent: DMF	DMF
Reaction Temperature: reflux (153°C)	184°→179°C (90 psi)
Yield: 14%	49%
Reaction Time: 40 hours	20 minutes



12a **12b**

(12) *Conventional*	*Microwave*
Solvent: DMF	DMF
Reaction Temperature: reflux (153°C)	183°→180°C (30 psi)
Yield: 24% of **12a**;	78% of **12a**;
5% of **12b**	17% of **12b**
Reaction Time: 5 hours	20 minutes



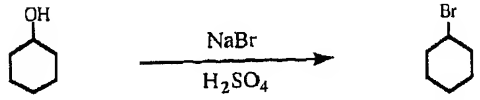
(13) *Conventional*	*Microwave*
Solvent: DMF	DMF
Reaction Temperature: reflux (153°C)	182°→178°C (15 psi)
Yield: 41%	69%
Reaction Time: 5 hours	20 minutes

of a mineral acid with a tertiary alcohol is so rapid that it is normally carried out by bubbling gaseous mineral acid into a cold solution of the alcohol. Since these reactions are often complete within a few minutes, we did not expect the reactions of tertiary alcohols to benefit from microwave heating. In contrast, the conversion of a primary or a secondary alcohol into an alkyl halide requires both higher reaction temperatures and longer reaction times, and these reactions should benefit from microwave heating. Indeed, the three transformations shown in Table 4 occur in only a few minutes using microwave procedures.

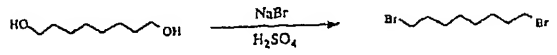
While control conditions indicated that thirty minutes were required to completely convert cyclohexanol to cyclohexyl bromide, this transformation occurs rapidly using microwave heating (Entry 15). Moreover, gas chromatography (GC) analysis has indicated that this reaction proceeds by first dehydration of the alcohol to produce

TABLE 4

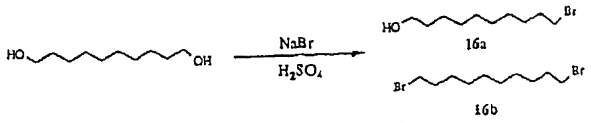
Conversion of Alcohols to Alkyl Bromides.



(14) *Conventional*	*Microwave*
Solvent: water	water
Reaction Temperature: reflux (118°C)	137°→140°C (10 psi)
Yield: 33%	49%
Reaction Time: 30 minutes	10 minutes



(15) *Conventional*	*Microwave*
Solvent: water	water
Reaction Temperature: reflux (118°C)	158°C (15 psi)
Yield: 70%	60%
Reaction Time: 20 minutes	30 seconds



(16) *Conventional*	*Microwave*
Solvent: water	water
Reaction Temperature: reflux (118°C)	156°→158°C (15 psi)
Yield: 23% of **16a**;	37% of **16a**;
3% of **16b**	24% of **16b**
Reaction Time: 30 minutes	30 seconds

cyclohexene, which then reacts with HBr to produce cyclohexyl bromide. This addition reaction involves a carbocation intermediate which can undergo polymerization and other side reactions resulting in low yields. Under microwave heating, the shorter reaction time minimizes these losses.

1,8-Octanediol (entry 15) is easily converted to the dibromide under both microwave and conventional conditions. The bromination of the homologous ten-carbon diol (Entry 16), however, is quite slow under conventional heating conditions due to the low solubility of the initial halohydrin product (cf. 16a) in the aqueous acid solvent system. Under microwave heating, dibromide 16b is obtained quickly. Here, which product is desired will influence the choice of heating method.

Finkelstein Reactions

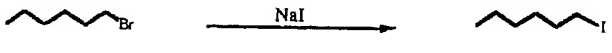
The classic Finkelstein procedure, a nucleophilic substitution reaction, is an equilibrium process. Alkyl iodides are prepared from alkyl chlorides by taking advantage of the fact that sodium chloride is insoluble in acetone. Thus, when an alkyl chloride or alkyl bromide is treated with sodium iodide in acetone to give an alkyl iodide, sodium chloride or sodium bromide precipitates out of the reaction mixture shifting the equilibrium in favor of alkyl iodide formation (Table 5). In our microwave experiments, we used 2-butanone rather than acetone as a solvent because its boiling point (80°C) is higher than that of acetone (56°C) and the higher temperatures result in shorter reaction times. The first two examples in Table 5 involve unhindered primary alkyl bromides and the advantage of microwave heating is modest. The reaction with the more hindered cyclohexyl bromide is extremely slow under reflux conditions but can be accomplished in a reasonable time using the microwave system.

Oxidations

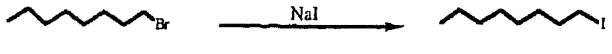
A common reaction of alcohols is their oxidation to produce carbonyl-containing compounds. Oxidation of primary alcohols gives aldehydes or carboxylic acids depending on the oxidant used, while secondary alcohols yield ketones. Tertiary alcohols do not react except under extremely vigorous conditions.

While most oxidations occur easily at ambient or low temperatures and would not benefit from microwave heating, we found that manganese dioxide oxidations are applicable to this new technology. Manganese dioxide is a mild oxidant which selectively oxidizes allylic and benzylic alcohols. A large excess of manganese dioxide is required for these oxidations as well as lengthy reaction times. Diethyl ether, the solvent of choice, does not efficiently absorb microwave radiation, so we carried out our microwave studies on these reactions in a quartz reaction vessel heated by a piece of ferrite (cf. Figure 1). In the three examples in Table 6, using microwave heating proved vastly superior for the oxidation in terms of both yield and reaction time. Each of these reactions is very clean, and although none go to completion regardless of heating period, the unreacted substrates can be recovered and recycled.

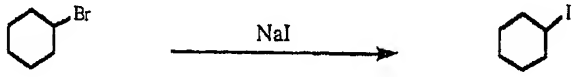
TABLE 5



(17)	Conventional	Microwave
Solvent:	2-butanone	2-butanone
Reaction Temperature:	reflux (80°C)	108°C (20 psi)
Yield:	81%	83%
Reaction Time:	40 minutes	4 minutes



(18)	Conventional	Microwave
Solvent:	2-butanone	2-butanone
Reaction Temperature:	reflux (80°C)	108°C (20 psi)
Yield:	78%	90%
Reaction Time:	30 minutes	10 minutes



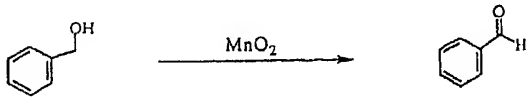
(19)	Conventional	Microwave
Solvent:	2-butanone	2-butanone
Reaction Temperature:	reflux (80°C)	131°→129°C (20 psi)
Yield:	80%	72%
Reaction Time:	80 hours	4 hours

Esterifications

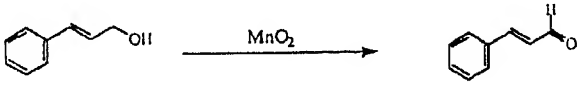
One important reaction of carboxylic acids is their conversion into esters. Although there are many procedures for accomplishing this transformation, the simplest method was discovered in 1895 by Fischer and Speier, wherein a carboxylic acid and an alcohol condense in the presence of a mineral acid catalyst. The need to use excess alcohol as solvent limits this method to the synthesis of simple esters; three examples are given in Table 7.

The esterification of benzoic acid requires over an hour of reflux, dramatically reduced to only one minute under microwave heating. The lengthy reaction time required for the

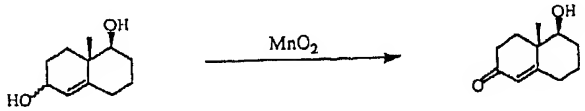
TABLE 6
Oxidations



(20)	*Conventional*	*Microwave*
Solvent:	diethyl ether	diethyl ether
Reaction Temperature:	reflux (36°C)	104°C (90 psi)
Yield:	20%	52%
Reaction Time:	8 hours	7 minutes

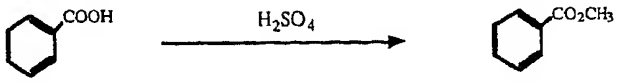


(21)	*Conventional*	*Microwave*
Solvent:	diethyl ether	diethyl ether
Reaction Temperature:	reflux (36°C)	116°C (90 psi)
Yield:	44%	82%
Reaction Time:	5 hours	3 minutes

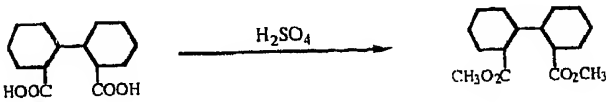


(22)	*Conventional*	*Microwave*
Solvent:	diethyl ether	diethyl ether
Reaction Temperature:	reflux (36°C)	103°C (90 psi)
Yield:	33%	79%
Reaction Time:	90 minutes	7 minutes

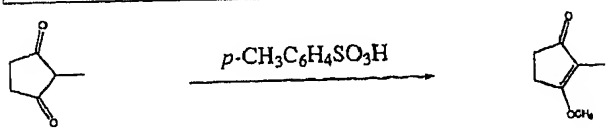
TABLE 7
Fischer Esterifications



(23)	*Conventional*	*Microwave*
Solvent:	methanol	methanol
Reaction Temperature:	reflux (65°C)	120°C (50 psi)
Yield:	92%	92%
Reaction Time:	80 minutes	1 minute



(24)	*Conventional*	*Microwave*
Solvent:	methanol	methanol
Reaction Temperature:	reflux (65°C)	118°→108°C (70 psi)
Yield:	80%	72%
Reaction Time:	80 hours	4 hours



(25)	*Conventional*	*Microwave*
Solvent:	methanol	methanol
Reaction Temperature:	reflux (65°C)	132°→136°C (90 psi)
Yield:	84%	86%
Reaction Time:	90 minutes	2 minutes

esterification shown in Entry 24 is because of the insolubility of the diacid in methanol. In this case much of the rate enhancement under microwave heating is probably due to increased solubility of the diacid at the higher reaction temperature.

Finally, the conversion of 2-methylcyclopentane-1,3-dione to 3-methoxy-2-methylcyclopentenone (Entry 25) is included as an esterification because a vinylogous ester is produced.

Hydrolyses

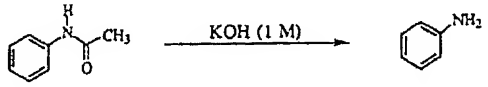
Esters, amides, and nitriles are hydrolyzed either by aqueous acid or aqueous base to the carboxylic acid and the corresponding alcohol or amine. The extensive heating usually required make these reactions ideal candidates for the application of microwave technology. All of these processes (Table 8) were efficiently achieved with dramatic rate enhancements using microwave heating. Note also the improved selectivity in the hydrolysis of 2-methylbenzonitrile (Entry 28). The initial product is amide 28b, which further hydrolyzes to the carboxylic acid. The amide product is obtained more selectively at the higher temperature due to greater rate enhancement of the first step.

The effect of steric hindrance on hydrolysis is clearly evident in the peptide hydrolyses studied. The isobutyl side chain of leucine makes glycyl-*d,l*-leucine as resistant to hydrolysis as unhindered glycyl-glycyl-glycine. Entry 31 shows the unreasonable reflux times needed for hydrolysis if both components of a dipeptide are hindered. These results suggest that microwave technology may be applicable to the digestion of biological samples [for recent examples, see Jassie, L. et al. [1994].

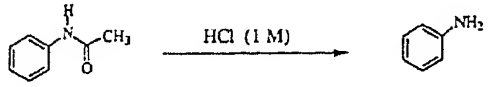
Williamson Ether Syntheses

The reaction of metal alkoxides with primary alkyl halides to form ethers is known as the Williamson ether synthesis and

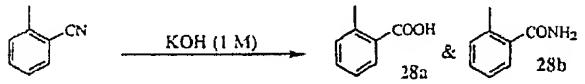
TABLE 8
Hydrolyses



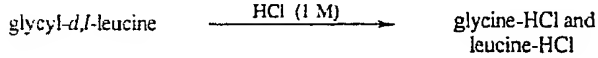
(26)	*Conventional*	*Microwave*
Solvent:	methanol - water	methanol - water
Reaction Temperature:	reflux (79°C)	130°→136°C (90 psi)
Yield:	60%	83%
Reaction Time:	36 hours	45 minutes



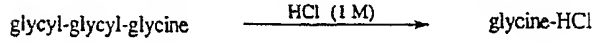
(27)	*Conventional*	*Microwave*
Solvent:	methanol - water	methanol - water
Reaction Temperature:	reflux (79°C)	141°→117°C (90 psi)
Yield:	98%	91%
Reaction Time:	4 hours	15 minutes



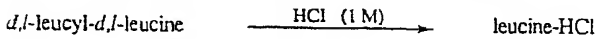
(28)	*Conventional*	*Microwave*
Solvent:	methanol - water	methanol - water
Reaction Temperature:	reflux (79°C)	130°C (90 psi)
Yield:	11% of **28a**; 70% of **28b**	5% of **28a**; 93% of **28b**
Reaction Time:	34 hours	15 minutes



(29)	*Conventional*	*Microwave*
Solvent:	water	water
Reaction Temperature:	reflux (100°C)	160°C (70 psi)
Yield:	73%	98%
Reaction Time:	12 hours	30 minutes



(30)	*Conventional*	*Microwave*
Solvent:	water	water
Reaction Temperature:	reflux (100°C)	156°C (90 psi)
Yield:	94%	98%
Reaction Time:	12 hours	15 minutes



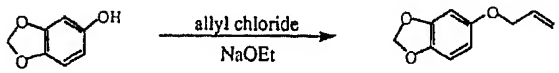
(31)	*Conventional*	*Microwave*
Solvent:	water	water
Reaction Temperature:	reflux (100°C)	158°C (70 psi)
Yield:	68%	89%
Reaction Time:	96 hours	3.5 hours

is recognized as the best way to make symmetrical and unsymmetrical ethers. Microwave heating proved superior to conventional heating in all cases studied (Table 9), most strikingly in the reaction of 2,6-dimethylphenol and allyl chloride. The steric effect of the methyl groups inhibits nucleophilic attack by the phenoxide on the allyl chloride, instead promoting deprotonation of ethanol (the solvent). The ethoxide anion generated *in situ* reacts with the allyl chloride present in the reaction mixture to account for the lower yields of the desired ether. Microwave heating improved the yield only modestly but greatly reduced the reaction time.

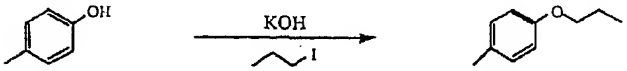
Aryl Methyl Ether Cleavage

Aryl methyl ethers can be readily cleaved by HBr using microwave heating (Table 10). The reaction proceeds by protonation of the ether oxygen followed by a nucleophilic attack on the methyl carbon by bromide. Electron-withdrawing

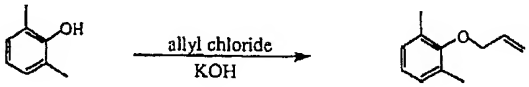
TABLE 9
Williamson Ether Syntheses.



(32)	*Conventional*	*Microwave*
Solvent:	ethanol	ethanol
Reaction Temperature:	reflux (78°C)	130°C (85 psi)
Yield:	89%	96%
Reaction Time:	60 minutes	1 minutes

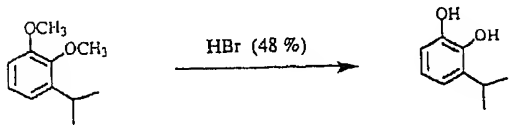


(33)	*Conventional*	*Microwave*
Solvent:	ethanol	ethanol
Reaction Temperature:	reflux (78°C)	131°C (90 psi)
Yield:	92%	96%
Reaction Time:	35 minutes	3 minutes

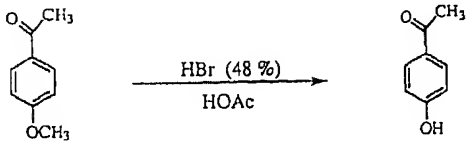


(34)	*Conventional*	*Microwave*
Solvent:	ethanol	ethanol
Reaction Temperature:	reflux (78°C)	131°C (90 psi)
Yield:	92%	96%
Reaction Time:	35 minutes	3 minutes

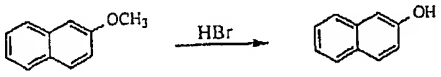
TABLE 10
Arl Ether Cleavage.



(35)	*Conventional*	*Microwave*
Solvent:	acetic acid	acetic acid
Reaction Temperature:	reflux (115°C)	152°→134°C (32 psi)
Yield:	97%	96%
Reaction Time:	3 hours	5 minutes



(36)	*Conventional*	*Microwave*
Solvent:	acetic acid	acetic acid
Reaction Temperature:	reflux (115°C)	170°→149°C (85 psi)
Yield:	47%	46%
Reaction Time:	52 hours	15 minutes



(27)	*Conventional*	*Microwave*
Solvent:	acetic acid	acetic acid
Reaction Temperature:	reflux (115°C)	156°→138°C (90 psi)
Yield:	81%	80%
Reaction Time:	72 hours	5 minutes

groups on the aryl ring decrease the basicity of the ether oxygen thereby retarding the reaction rate (cf. Entry 36).

The demethylation of β-naphthyl methyl ether (Entry 37) is very slow under conventional heating because the substrate is virtually insoluble in acetic acid. This is the second reaction (cf. Entry 24) for which the observed rate enhancement under microwave heating is most likely due to the increased solubility of the reactant at higher reaction temperatures.

Miscellaneous Reactions

This final section presents examples of other common reactions that can be carried out efficiently using microwave heating. The first three examples shown in Table 11 involve the base-promoted migration of a double bond into a more stable conjugated position; entries 39 and 40 also involve a subsequent tautomerization. While we were able to reproduce the published results for entries 38 [Chapman et al., 1971] and 39 [Davey and Hearne, 1964], in our hands the rearrangement of (E)-1-phenyl-2-buten-1-ol to butyrophenone (**40a**) failed [Iqbal and Jackson, 1968]. Instead, we obtained products which were derived from nucleophilic attack by anions of the solvent.

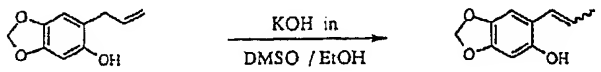
Several "Name Reactions" were also studied. The Beckmann rearrangement, the acid-catalyzed rearrangement of an oxime to an amide, is quite general in scope and clearly benefits from microwave heating (Entry 41). The condensation of the malonate derivative with urea in Entry 42 yields a barbituric acid derivative in high yield after only six minutes of heating. Most Friedel-Crafts alkylations are conducted at or below room temperature by using strong Lewis or protic acids but entry 43 is an exception which proceeds rapidly under mild acid conditions in a microwave oven. The Fischer indole synthesis, a powerful method for making indoles, involves the loss of ammonia from an arylhydrazone of an aldehyde or ketone when treated with an acid catalyst (cf. Entry 44). This reaction has been investigated by others using various conditions and microwave heating [Manhas et al, 1991; Abramovitch, 1992]. Finally, alkyl bromides react with magnesium to form Grignard reagents. However, in Example 45, formation of the Grignard reagent results in an elimination and ring opening.

Conclusions

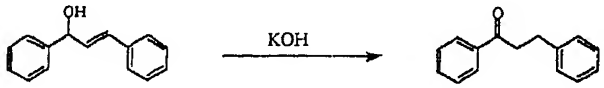
In organic chemistry a common rule of thumb is that the reaction rate for most reactions doubles for every ten degrees (°C) increase in the reaction temperature. This tenet is based on the Arrhenium equation. Since chemical kinetics are independent of the mode of heating and given the large sampling of reactions provided, an obvious equestion is: "How does the observed reaction rates using microwave heating compare to that observed using conventional methods ?" This data is summarized is Table 12. While no effort was made to optimize our microwave results, it is significant that thirty-three of the forty-five experiments carried out fall within simple Arrhenius expectations. We believe that further work would confirm that each of the twelve experiments which either exceed or occur at a rate less than that predicted would ultimately be found to conform with simple Arrhenius approximations.

The use of microwave heating in organic synthesis is still in its infancy. These transformations demonstrate that a large number of fundamental organic reactions occur more

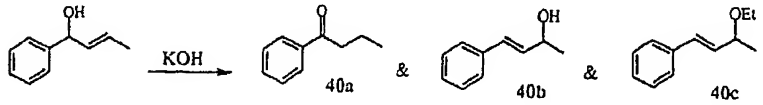
TABLE 11
Miscellaneous Reactions



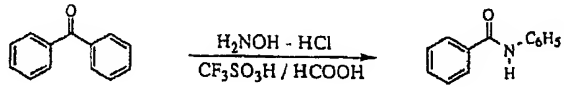
(38)	Conventional	Microwave
Solvent:	CMSO/ethanol	DMSO/ethanol
Reaction Temperature:	reflux (109°C)	170°C (41 psi)
Yield:	90%	80%
Reaction Time:	4 hours	3 minutes



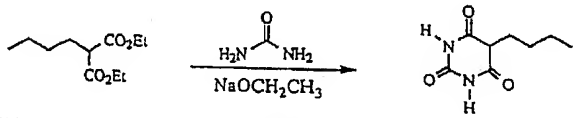
(39)	Conventional	Microwave
Solvent:	ethanol - water	ethanol - water
Reaction Temperature:	reflux (83°C)	145°C (90 psi)
Yield:	86%	97%
Reaction Time:	20 hours	10 minutes



(40)	Conventional	Microwave
Solvent:	ethanol/water	ethanol/water
Reaction Temperature:	reflux (83°C)	146°→144°C (90 psi)
Yield:	trace **40a**; 6% of **40b**; 2% of **40C**	2.4% of **40a**; 39% of **40b**; 16% of **40C**
Reaction Time:	4 days	10 minutes

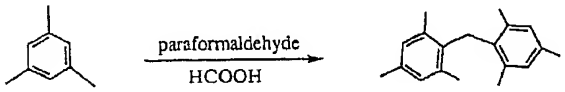


(41)	Conventional	Microwave
Solvent:	formic acid	formic acid
Reaction Temperature:	reflux (101°C)	171°C (90 psi)
Yield:	96%	99%
Reaction Time:	90 minutes	3 minutes

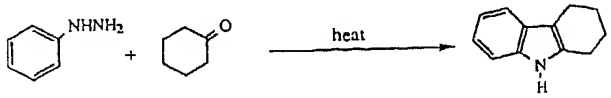


(42)	Conventional	Microwave
Solvent:	ethanol	ethanol
Reaction Temperature:	reflux (78°C)	142°C (90 psi)
Yield:	63%	80%
Reaction Time:	120 minutes	6 minutes

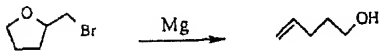
(Table 11 continued)



(43)	*Conventional*	*Microwave*
Solvent:	HCOOH	HCOOH
Reaction Temperature:	reflux (01°C)	130°→152°C (26 psi)
Yield:	72%	75%
Reaction Time:	90 minutes	4 minutes



(44)	*Conventional*	*Microwave*
Solvent:	CH_3COOH	CH_3COOH
Reaction Temperature:	reflux (118°C)	118°C (46 psi)
Yield:	100%	100%
Reaction Time:	15 minutes	2 minutes



(45)	*Conventional*	*Microwave*
Solvent:	diethyl ether	diethyl ether
Reaction Temperature:	reflux (36°C)	106°→105°C (90 psi)
Yield:	44%	38%
Reaction Time:	3 hours	10 minutes

rapidly and in comparable yield using microwave heating rather than conventional heating procedures. Not surprisingly, we expect this area to continue to be the focus of extensive activity.

Experimental Section

General Procedures

All solvents were distilled prior to use. Ether implies diethyl ether except when otherwise specified.

Standard ethereal workup consisted of partitioning the reaction mixture between ether and water, and then drying the organic phase with a saturated brine wash and then over anhydrous magnesium sulfate. The resulting solution was concentrated to a residue at water aspirator pressure. Chromatography was performed on silica gel. In each control experiment the workup, isolation, and analytical procedures used in the original were duplicated.

Acid-washed activated MnO_2 used in the oxidation studies was prepared by the method of Harfenist et al. [1954]. The diene used in Entry 12 was prepared by the Birch reduction of *o*-xylene. The propargylic alcohol used in Entry 9 was prepared by acetylenide addition to 6-methyl-5-hepten-2-one. The diene used in Entry 5 was obtained by treating cyclohexanone with vinyl magnesium bromide and subsequently dehydrating the resulting alcohol with phosphoric acid. The diol used in Entry 22 was obtained by lithium aluminum hydride reduction of Weland-Miescher ketone, prepared by the procedure of Ramachandran and Newman [1973]. Preparations for the alcohols used in Entries 36 and 37 are found in the literature [Davey and Hearne, 1964, respectively]. The tetrahydrofurfuryl bromide used in Entry 44 was prepared from the corresponding alcohol by treatment with PBr_3. Other compounds were obtained from commercial sources.

Where compositions of mixtures are given from ^1H NMR analysis, spectra were taken at 250 or 300 MHz and the molar ratios of the components were determined by integrating convenient, fully resolved signals and converting to the appropriate mass percent; where mass and net yield figures follow, these were calculated from the mass percent.

The following abbreviations are used: DMF for dimethylformamide, DMSO for dimethylsulfoxide, THF for tetrahydrofuran, and psi for pounds per square inch gauge.

Example (1). 1,4-Diphenyl-1,3-butadiene (1.00 g, 4.85 mmol) and diethyl acetylenedicarboxylate (1.23 g, 7.23 mmol) in DMF (15 mL) were heated at 70% power to 30 psi. This pressure was maintained for twenty minutes during which time the reaction temperature declined from 198°C to 194°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the crude residue was chromatographed (hexanes-ether, 20:1, followed by 10:1) to isolate the adduct as a pale yellow solid (1.05 g, 58%).

In a control experiment, an identical reaction mixture required six hours of reflux (oil bath) for completion. Identical workup and chromatography gave 1.22 g (67%) of the adduct.

Example (2). Furan (2.00 g, 29.41 mmol) and diethyl acetylenedicarboxylate (1.00 g, 5.88 mmol) in DMF (15 mL) were heated at 80% power to 30 psi. This pressure was maintained for ten minutes during which time the reaction temperature declined from 163°C to 147°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the crude residue was chromatographed (hexanes-ether, 10:1) to give an amber colored oil (1.20 g, 86%).

The control experiment was performed on a reduced scale (diethyl acetylenedicarboxylate: 143 mg, 0.84 mmol; furan: 286 mg, 4.20 mmol; DMF: 2 mL) in a sealed tube. The reaction vessel was placed in a preheated oil bath maintained for

TABLE 12

Example	Conventional Time (minutes)	Microwave Time (minutes)	Initial Ratio	Arrhenius Factor	Corrected Ratios	
1	360	20	18	19.7	0.91	N
2	15	10	1.5	0.25	6.00	P
3	45	4	11.3	13	0.87	N
4	120	12	10	18.4	0.54	N
5	60	30	2	19.7	0.10	M
6	4800	300	40	18.4	2.17	N
7	2160	5	432	18.4	23.48	P
8	5760	20	288	18.4	15.65	P
9	5760	480	12	21.1	0.57	N
10	20	1	20	24.2	0.83	N
11	2400	20	120	7.5	16.00	P
12	300	20	15	7.2	2.08	N
13	300	20	15	6.5	2.31	N
14	30	10	3	4	0.75	N
15	20	0.5	40	16	2.50	N
16	30	0.5	60	15	4.00	N
17	40	4	10	7	1.43	N
18	30	10	3	7	0.43	N
19	4800	240	20	32	0.63	N
20	480	7	69	111	0.62	N
21	300	3	100	256	0.39	N
22	90	7	12.9	104	0.12	M
23	80	1	80	45	1.78	N
24	2520	30	84	27	3.11	N
25	90	2	45	119	0.38	N
26	2160	45	48	42	1.14	N
27	240	15	16	32	0.50	N
28	2040	15	136	34	4.00	N
29	720	30	24	64	0.38	N
30	720	15	48	49	0.98	N
31	5760	210	27	60	0.45	N
32	60	1	60	37	1.62	N
33	35	3	12	40	0.30	N
34	210	4	52	28	1.86	N
35	180	5	36	7	5.14	P
36	3120	15	2108	22	9.45	P
37	4320	5	864	12	72.00	P
38	240	3	80	69	1.16	N
39	1200	10	120	73.5	1.63	N
40	5760	10	576	73.5	7.84	P
41	90	3	30	128	0.23	N
42	120	6	20	42.2	0.47	N
43	90	4	22.5	10.5	2.14	N
44	15	2	7.5	52	0.14	M
45	180	10	18	119	0.15	M

at 175 °C for fifteen minutes. Identical workup and chromatography gave 135 mg (68%) of the adduct.

Example (3). Anthracene (2.00 g, 11.20 mmol) and maleic anhydride (1.00 g, 10.20 mmol) in DMF (25 mL) were heated at 70% power to 15 psi. The temperature remained constant at 190°C while this pressure was maintained for four minutes. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the crude residue was recrystallized from xylenes to give colorless needles (2.60 g, 84%).

As the control, an identical reaction mixture was refluxed for forty-five minutes (oil bath). Identical workup and purification gave 2.65 g (86%).

Example (4). Anthracene (1.85 g, 10.38 mmol) and dimethyl fumarate (1.00 g, 6.94 mmol) in DMF (15 mL) were heated at 80% power to 20 psi. This pressure was maintained for twelve minutes during which time the temperature declined from 197 °C to 192 °C. The vessel was cooled, the contents were diluted with brine and then extracted twice with a mixture of THF and ether (1:1). The combined organic phases were washed with water, dried over anhydrous magnesium sulfate and concentrated at reduced pressure. Unreacted diethyl fumarate was removed from the residue by heating two hours at 60°C and 0.5 mm pressure. The Diels-Alder adduct, which proved inseparable chromatographically from unreacted anthracene, was saponified by refluxing overnight with 2 g of KOH in THF (10 mL) and water (5 mL). This mixture was diluted with ether, then extracted with 5% aqueous NaOH. The combined aqueous phases were washed with ether, then acidified to pH < 2 with concentrated HCl, and extracted with ether. The organic phase was washed with water, dried over anhydrous magnesium sulfate, and concentrated. Residual THF was removed by heating for six hours at 75 °C at 1 mm. The diacid remained as a white solid (1.54 g, 75%).

As the control, an identical reaction mixture was refluxed for two hours (oil bath). The diacid (1.67 g, 82%) was obtained by the same workup, saponification, and isolation procedures.

Example (5). 1-Vinylcyclohexene (1.00 g, 9.26 mmol) and diethyl oxomalonate (0.80 g, 4.63 mmol) in DMF (15 mL) were heated at 70% power to 23 psi. This pressure was maintained for thirty minutes during which time the reaction temperature declined from 198 °C to 192 °C. The reaction mixture was then cooled to 0 °C. After standard ethereal workup the crude residue was chromatographed (hexanes-ether, 10:1) to isolate the adduct (744 mg, 57%) as a colorless oil.

As the control, an identical mixture was refluxed using an oil bath for a one-hour period. The same workup and isolation procedures gave 713 mg (55%) of adduct.

Example (6). Allyl phenyl ether (1.00 g, 7.45 mmol) in DMF (15 mL) was heated at 70% power to 30 psi. This pressure was maintained for five hours during which time the reaction temperature declined from 198°C to 193°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the residue was chromatographed (hexanes-ether, 20:1 followed by 3:1) to give *o*-allylphenol (800 mg, 80%).

As the control, an identical reaction mixture was refluxed for eighty hours (oil bath). The same workup and isolation procedures gave 230 mg (23%) of the rearrangement product.

Example (7). Sesamol allyl ether (5.12 g, 28.82 mmol) in DMF (10 mL) was heated at 50% power to 30 psi. This pressure was maintained for five minutes during which time the reaction temperature remained at 195°C. After cooling, the mixture was diluted with water and extracted with ether. The organic phase was extracted with 5% NaOH, and the resulting aqueous solution was acidified to pH < 2 by addition of concentrated HCl and extracted with ether. This ethereal solution was dried over anhydrous magnesium sulfate and concentrated to give allylsesamol (4.96 g, 97%) as an amber-colored oil.

As the control, an identical mixture was refluxed for thirty-six hours (oil bath). Identical isolation procedures gave 2.08 g (72%) of allylsesamol.

Example (8). Allyl 2,6-dimethylphenyl ether (2.00 g, 12.30 mmol) in DMF (15 mL) was heated at 70% power to 17 psi. This pressure was maintained for twenty minutes during which time the reaction temperature declined from 197°C to 192°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the crude residue was chromatographed (hexanes followed by hexanes-ether 10:1) to obtain the rearrangement product (1.81 g, 91%) as a colorless oil.

As a control experiment, an identical mixture was refluxed for four days (oil bath). Identical isolation gave 1.65 g (83%) of adduct.

Example (9). 3,7-Dimethyl-6-octen-1-yn-3-ol (1.00 g, 6.57 mmol) in DMF (15 mL) was heated at 70% power to 23 psi. This pressure was maintained for eight hours during which time the reaction temperature declined from 198°C to 196°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the crude residue was chromatographed. The diastereomeric cyclopentanols [328 mg (33%) and 115 mg (40%) in order of elution] were isolated as colorless oils by chromatography (hexanes-ether, 40:1 gradient to 4:1). Relative configurations were not assigned.

As the control, an identical reaction mixture was refluxed for four days using an oil bath, although TLC analysis indicated the reaction was not complete. The same products [151 mg (15%) and 181 mg (18%) in order of elution] were isolated by the same procedures.

Example (10). β-Pinene (1.00 g, 7.34 mmol) and diethyl ketomalonate (2.55 g, 14.68 mmol) in DMF (15 mL) were heated at 70% power to 20 psi. This pressure was maintained for one minute during which time the reaction temperature remained at 199°C. The reaction mixture was then cooled to 0°C and standard ethereal workup gave 1.83 g of a crude residue. Chromatography (hexanes followed by hexanes-ether, 10:1) provided 1.62 g of adduct (71%) as a colorless oil.

As the control, an identical mixture was refluxed for twenty minutes (oil bath). Identical workup and isolation gave 1.55 g (68%) of adduct.

Example (11). Diethyl acetylenedicarboxylate (0.50 g, 3.52 mmol), 1,4-cyclohexadiene (4.23 g, 52.82 mmol) and DMF (5 mL) were heated at 100% power to 90 psi. This pressure was maintained for twenty minutes during which time the reaction temperature declined from 184°C to 179°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, solvent removal and recovery of excess 1,4-cyclohexadiene were accomplished by means of fractional distillation. The remaining residue was chromatographed (hexanes-ether, 20:1 followed by 10:1) to give the tricyclic product (386 mg, 49%) as a colorless oil.

As the control, an identical reaction mixture was refluxed for forty hours using an oil bath, however, TLC analysis indicated that the reaction was not complete. Identical workup and isolation procedures gave 108 mg (14%) of tricyclic product.

Example (12). Diethyl acetylenedicarboxylate (0.50 g, 3.52 mmol), 1,2-dimethyl-1,4-cyclohexadiene (5.71 g, 52.82 mmol) and 5 mL of DMF were heated at 100% power to 30 psi. This pressure was maintained for twenty minutes during which time the reaction temperature declined from 183°C to 180°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the excess diene was recovered as described in Example 11. The remaining residue was chromatographed (hexanes-ether, 20:1 followed by 10:1) to isolate 12a (690 mg, 78%) as a colorless oil. Fractions containing 12b plus an impurity inseparable in the hexanes-ether system were rechromatographed (hexanes-ethyl acetate, 10:1) to isolate 150 mg (17%) of 12b as a colorless oil.

As the control, an identical mixture was refluxed for five hours (oil bath). Adducts 12a (240 mg, 24%) and 12b (50 mg, 5%) were isolated by means of the same isolation procedures.

Example (13). Diethyl acetylenedicarboxylate (0.50 g, 3.52 mmol), bicyclo[4.3.0]nona-3,6(1)-diene (7.47 g of commercially available 85%, 53.00 mmol) and DMF (5 mL) were heated at 100% power to 15 psi. This pressure was maintained for twenty minutes during which time the reaction temperature declined from 182°C to 178°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup, the crude residue was chromatographed (hexanes-ether, 20:1 followed by 10:1 then 5:1) to isolate the tetracyclic adduct as a colorless oil (634 mg, 69%). The excess diene was recovered from the early fractions.

As the control, an identical reaction mixture was refluxed for five hours (oil bath). Identical workup and purification gave 380 mg (41%) of the adduct.

Example (14). Cyclohexanol (2.00 g, 20.00 mmol) was added to a solution of NaBr (3.10 g, 30.12 mmol) in 7 mL of concentrated H_2SO_4 and 7 mL of water. The mixture was heated at 70% power to 10 psi. This pressure was maintained for ten minutes during which time the reaction temperature rose from 137°C to 140°C. After cooling, the mixture was diluted with water and extracted with hexanes. The organic phase was washed with brine containing a trace of $NaHSO_3$ and dried over anhydrous $MgSO_4$. Removal of the volatiles under reduced pressure gave cyclohexyl bromide (1.60 g, 49%) as an amber-colored oil.

As the control an identical mixture was refluxed for thirty minutes (oil bath). Identical isolation procedures gave 1.09 g (33%).

Example (15). 1,8-Octanediol (1.00 g, 6.85 mmol) was added to a solution of NaBr (2.12 g, 20.61 mmol) in 7 mL of concentrated H_2SO_4 and 7 mL of water. The mixture was heated at 70% power to 15 psi. This pressure was maintained for thirty seconds during which time the reaction temperature remained at 158°C. The dibromide (1.12 g, 60%) was isolated as described in example 14.

As the control, an identical mixture was refluxed for twenty minutes (oil bath). Identical workup gave 1.30 g of dibromide (70%).

Example (16). 1,10-Decanediol (1.00 g, 5.74 mmol) was added to a solution of NaBr (1.48 g, 14.3 mmol) in 7 mL of concentrated H_2SO_4 and 7 mL of water. The mixture was heated at 100% power to 15 psi. This pressure was maintained for thirty seconds during which time the reaction temperature increased from 156°C to 158°C. The reaction mixture was then cooled to 0°C. After standard ethereal workup,

the crude residue was chromatographed (hexanes followed by hexanes-ether 1:1) to isolate bromide 16a (643 mg, 37%) and dibromide 16b (406 mg, 24%) as colorless oils.

As a control experiment, an identical mixture was refluxed for thirty minutes using an oil bath and subjected to identical workup and separation techniques to give 310 mg (23%) of 16a and 57 mg (3%) of 16b.

Example (17). 1-Bromohexane (2.35 g, 14.22 mmol) was added to a solution of NaI (3.20 g, 21.4 mmol) in 2-butanone (20 mL). The mixture was heated at 70% power to 20 psi and 108°C. These conditions were maintained for four minutes. After cooling, the mixture was diluted with water and extracted with ether. The organic phase was washed with water containing a trace of $NaHSO_3$ and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to leave the iodide (2.51 g, 83%) along with a trace (< 1% by ^1H NMR analysis) of unreacted 1-bromohexane.

As the control, an identical mixture was refluxed (oil bath) while monitored by GC analysis. Conversion was 99% complete after forty minutes. Identical workup gave 2.45 g (81%) containing < 1% of unreacted bromide (^1H NMR analysis).

Example (18). 1-Bromooctane (2.24 g, 11.60 mmol) was added to a solution of NaI (2.60 g, 17.40 mmol) in 20 mL of 2-butanone. The mixture was heated at 70% power to 20 psi and 108 °C for a ten-minute period. After cooling, the mixture was diluted with water and extracted with ether. The organic phase was washed with brine containing a trace of $NaHSO_3$ and dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure to leave the iodide (2.50g, 90%).

As the control, an identical reaction mixture was refluxed (oil bath) while monitored by GC analysis. Conversion was 99% complete after thirty minutes. Identical workup gave 2.17 g of iodide (78%).

Example (19). Cyclohexyl bromide (2.65 g, 16.33 mmol) was added to a solution of NaI (3.65 g, 24.44 mmol) in 20 mL of 2-butanone. The mixture was heated at 70% power to 20 psi. This pressure was maintained for four hours during which time the temperature decreased from 131°C to 129°C. The reaction mixture was then cooled to 0°C. The workup used in Example 18 gave 3.02 g of cyclohexyl iodide (72% net yield) of 85% purity (^1H NMR analysis).

As a control, an identical mixture was refluxed (oil bath) while monitored by GC analysis. After eighty hours significant cyclohexyl bromide was still present. Identical workup gave 3.00 g (72% net yield) of 85% purity (^1H NMR analysis).

Example (20). Benzyl alcohol (0.50 g, 4.60 mmol) and activated MnO_2 (2.00 g, 23.00 mmol) were placed in a quartz vessel (cf. Figure 1). After purging with dry nitrogen, anhydrous ether (10 mL) was introduced by syringe. The mixture was heated at 20% power to 90 psi and 104°C. These conditions were maintained for seven minutes. After cooling, the oxidant was removed by filtration through Celite and the solvent was removed at reduced pressure. Pure benzaldehyde (254 mg, 52%) and unreacted starting material were isolated by chromatography (hexanes-ether, 10:1).

As a control experiment, an identical mixture was refluxed for eight hours using an oil bath and separated to give 102 mg (20%) of benzaldehyde and the balance of the starting material.

Example (21). *trans*-Cinnamyl alcohol (0.50 g, 3.70 mmol) and activated MnO_2 (2.00 g, 23.00 mmol) were placed in a quartz reaction vessel (cf. Figure 1). After purging with nitrogen, anhydrous ether (10 mL) was introduced by syringe. The mixture was heated at 20% power to 90 psi and 116°C. These conditions were maintained for three minutes. The reaction mixture was then cooled to 0°C. The oxidant was removed by filtration through Celite and the solvent was removed at reduced pressure. *trans*-Cinnamaldehyde (402 mg, 82%) and the balance of the starting material were separated by column chromatography (hexanes-ether, 10:1).

As the control, an identical mixture was refluxed for five hours (oil bath) and separated to give 219 mg (44%) of the aldehyde and the balance of the starting material.

Example (22). 1,2,3,4,6,7,8,8a-Octahydro-8a-methyl-1,6-naphthalenediol (200 mg, 1.10 mmol) and activated MnO_2 (2.00 g, 23.00 mmoL) were placed in a quartz reaction vessel (Figure 1). After purging with dry nitrogen, anhydrous ether (10 mL) was introduced by syringe. The mixture was heated at 20% power to 90 psi. This pressure was maintained for seven minutes during which time the temperature was constant at 103°C. The enone product (157 mg, 79%) and the balance of the starting material were separated by column chromatography (hexanes-ether, 4:1 followed by 1:1).

As the control, an identical reaction mixture was refluxed for ninety minutes (oil bath) and separated as above to give 66 mg (33%) of the product and the balance of the starting material.

Example (23). Benzoic acid (6.1 g, 49.18 mmol) was added to a mixture of concentrated H_2SO_4 (2 mL) and 25 mL of methanol. The reaction mixture was heated at 20% power to 50 psi for one minute during which time the reaction temperature was maintained at 120°C. Standard ethereal workup gave 6.23 g of methyl benzoate (92%).

As the control, an identical mixture was refluxed for eighty minutes using an oil bath and worked up to give 6.24 g (92%) of the ester.

Example (24). 2,2'-Bis(cyclohexanecarboxylic acid) (500 mg, 19.72 mmol) was added as a powder to a mixture of concentrated H_2SO_4 (0.5 mL) and methanol (5 mL). The diacid proved almost totally insoluble in this mixture. The mixture was heated at 35% power to 70 psi for thirty minutes during which time the reaction temperature declined from 118°C to 108°C. Standard ethereal workup gave the diester (470 mg, 85%) as a white crystalline solid.

In a control experiment, an identical mixture was refluxed for forty-two hours using an oil bath. Identical workup gave 537 mg (97%) of the diester.

Example (25). 2-Methyl-1,3-cyclopentandione (2.00 g, 18.23 mmol) was added to a solution of *p*-toluenesulfonic acid (100 mg, 0.53 mmol) in 15 mL of methanol. The mixture was heated at 70% power to 90 psi for two minutes during which time the reaction temperature rose from 132°C to 136°C. The mixture was cooled with brine and extracted with methylene chloride (4 x 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, dried over anhydrous magnesium sulfate and concentrated. The residue was chromatographed (methylene chloride-methanol, 10:1) to isolate the vinylogous ester (1.93 g, 86%).

As the control, an identical mixture was refluxed for ninety minutes (oil bath). Identical workup and isolation procedures gave 1.89 g (84%) of the cyclopentenone.

Example (26). Acetanilide (1.00 g, 7.41 mmol) was added to a 1 N solution (20 mL) of KOH in methanol-water (1:1). The mixture was heated at 35% power to 90 psi. This pressure was maintained for forty-five minutes during which time the reaction temperature increased from 130°C to 136°C. Standard ethereal workup, followed by chromatography, gave 571 mg of aniline (83%).

As the control, an identical mixture was refluxed thirty-six hours using an oil bath and worked up to give 413 mg (60%) of aniline.

Example (27). Acetanilide (1.00 g, 7.41 mmol) was added to a 1 N solution of HCl (20 mL) in methanol-water (1:1). The mixture was heated at 35% power to 90 psi. This pressure was maintained for 15 minutes during which time the reaction temperature declined from 141°C to 117°C. The cooled mixture was neutralized with saturated aqueous $NaHCO_3$. Standard ethereal workup, followed by chromatography, gave 628 mg (91%) aniline.

As the control, an identical mixture was refluxed for four hours (oil bath) and worked up to give 679 mg (98%) of aniline.

Example (28). *o*-Toluonitrile (1.00 g, 8.55 mmol) was added to a 1 N solution (20 mL) of KOH in methanol-water (1:1). The mixture was heated at 35% power to 90 psi. This pressure was maintained for fifteen minutes during which time the reaction temperature remained at 130°C. The cooled mixture was diluted with saturated brine, acidified (pH < 2 by the addition of concentrated HCl) and extracted with methylene chloride (3 x 30 mL). The combined organic extracts were dried over anhydrous mangesium sulfate and concentrated to give a white solid (1.13 g) consisting of *o*-toluamide (95% by ^{1}H NMR analysis, 107 mg, 93% net yield) and *o*-toluic acid (5% by ^{1}H NMR analysis, 57 mg, 5% net yield).

An identical reaction mixture was refluxed for thirty-four hours using an oil bath and gave a mixture (935 mg) of the amide (86% by ^{1}H NMR analysis, 804 mg, 70% net yield) and the acid (14% by ^{1}H NMR analysis, 131 mg, 11% net yield.)

Example (29). Glycyl-*d,l*-leucine (200 mg, 1.06 mmol) was dissolved in 1 N aqueous HCl (10 mL). The solution was heated at 70% power to 70 psi. This pressure was maintained for thirty minutes during which time the reaction temperature was constant at 160°C. The mixture was lyophilized to constant weight (290 mg, 98%) at < 1mm pressure.

As the control, an identical mixture was refluxed for twelve hours (oil bath). Using the same workup procedure gave 216 mg (73%) of amino acid salts.

Example (30). Glycylglycylglycine (200 mg, 1.06 mmol) was dissolved in 1 N aqueous HCl (10 mL). The solution was heated at 70% power to 90 psi. This pressure was maintained for fifteen minutes during which time the reaction temperature remained at 156°C. The mixture was lyophilized to constant weight (348 mg, 98%) at < 1mm pressure.

As the control, an identical solution was refluxed for twelve hours using an oil bath. The use of conventional heating gave 331 mg (94%) of hydrochloride salts.

Example (31). *d,l*-Leucyl-*d,l*-leucine (200 mg, 0.82 mmol) was dissolved in 1 N aqueous HCl (10 mL). The solution was heated at 70% power to 70 psi. This pressure was maintained for 3 and a half hours during which time the reaction temperature increased from 158°C to 160°C. The mixture was lyophilized to constant weight (243 mg, 89%) at < 1mm.

As the control, an identical mixture was refluxed for ninety-six hours (oil bath). The same workup procedure as described above yielded 185 mg (68%) of leucine hydrochloride salt.

Example (32). Sodium (0.49 g, 21.30 mmol) was dissolved in 13 mL of absolute ethanol under nitrogen. The solution was transferred to the microwave vessel which was then sealed. A solution of sesamol (2.50 g, 18.00 mmol) in absolute ethanol (5 mL) followed by allyl chloride (2.10 g, 27.03 mmol) was added by syringe through one of the tubing fittings. The mixture was heated at 35% power to 85 psi. This pressure was maintained for one minute during which time the reaction temperature remained at 130°C. The cooled mixture was diluted with water and extracted with ether. The combined organics were washed with 5% aqueous NaOH, water, dried over anhydrous magnesium sulfate and concentrated to give the ether (3.11 g, 96%) as a light brown oil.

As the control, an identical mixture was refluxed for one hour (oil bath). Identical isolation procedures gave 2.88 g (89%) of the desired ether.

Example (33). *p*-Cresol (2.22 g, 20.55 mmol) and propyl iodide were added to alcoholic KOH (15 mL, 10% w/v) and the mixture was heated at 70% power to 90 psi. This pressure was maintained for three minutes during which time the reaction temperature was constant at 131 °C. After standard ethereal workup, the crude residue was chromatographed (hexanes-ether, 10:1) to give the ether (2.96 g, 96%) as a colorless oil.

As the control, an identical mixture was refluxed for thirty-five minutes using an oil bath. Identical workup and purification gave 2.84 g (92%) of the desired ether.

Example (34). 2,6-Dimethylphenol (5.00 g, 40.98 mmol) and allyl chloride (4.69 g, 61.47 mmol) were added to a solution of KOH (2.75 g, 49.16 mmol) in 20 mL of methanol. The mixture was heated at 70% power to 90 psi. This pressure was maintained for four minutes during which time the reaction temperature was constant at 126°C. The cooled mixture, which was not basic and contained some unreacted phenol, was worked up using ether and chromatographed (elution with hexanes) to provide the ether (4.60 g, 69%) as a colorless oil.

As the control, an identical mixture was refluxed for three and one half hours (oil bath). Identical workup and chromatography gave 4.17 g (63%) of the ether.

Example (35). 3-Isopropylveratrole (500 mg, 2.77 mmol) was added to a mixture of 10 mL of aqueous (48%) HBr and 10 mL of acetic acid. The mixture was heated at 100% power to 32 psi for five minutes during which time the reaction temperature declined from 152°C to 134°C. Following standard ethereal workup, the crude residue was chromatographed (hexanes-ether, 10:1) and provided 407 mg of the catechol (96%).

As the control, an identical mixture was refluxed for three hours (oil bath). Identical isolation gave 409 mg (97%) of catechol.

Example (36). *p*-Methoxyacetophenone (2.00 g, 13.33 mmol) was added to a mixture of 10 mL of aqueous (48%) HBr and 10 mL of acetic acid. The mixture was heated at 100% power to 85 psi and maintained for fifteen minutes during which time the reaction temperature declined from 170°C to 149°C. After standard ethereal workup the residue was chromatographed (hexanes-ether, 5:1 gradient to 1:1) to give the phenol (840 mg, 46%).

As the control, an identical mixture was refluxed for fifty-two hours (oil bath). Identical isolation gave 869 mg (47%).

Example (37). β-Naphthyl methyl ether (2.00 g, 12.64 mmol) was added to a mixture of 10 mL of aqueous (48%) HBr and 10 mL of acetic acid. The mixture was heated at 100% power to 90 psi and maintained for five minutes, during which time the reaction temperature declined from 156°C to 138°C. After standard ethereal workup the residue was chromatographed (hexanes-ether, 5:2) to give 1.45 g of β–naphthol (80%).

As the control, an identical mixture was refluxed for seventy-two hours (oil bath). Identical isolation gave 1.47 g (81%) of β-naphthol.

Example (38). 2-Allyl sesamol (200 mg, 1.12 mmol) in DMSO (10 mL) was added to a solution of KOH (500 mg, 8.90 mmol) in 5 mL of ethanol. The mixture was heated at 35% power to 41 psi for three minutes during which time the reaction temperature remained at 170°C. The cooled mixture was acidified (pH < 2) by the addition of concentrated HCl and extracted with ether. Standard ethereal workup gave 178 mg of crude residue which was purified by chromatography (hexanes-ether, 1:1) to give the isomerized product (160 mg, 80%) as light-brown crystals.

An identical mixture was refluxed for four hours using conventional heating (oil bath) and subjected to identical workup and chromatography to give 179 mg (90%) of the same product. In both cases a negligible trace of unreacted starting material remained which proved chromatographically inseparable from the product.

Example (39). Chalcol (1.00 g, 4.76 mmol) was added to a solution (25 mL) of KOH (20%, w/v) in aqueous ethanol (60%, v/v). The mixture was heated at 100% power to 90 psi for ten minutes during which time the reaction temperature remained at 145°C. The cooled mixture was acidified (pH < 2) by the addition of concentrated HCl. Standard ethereal workup gave 965 mg (97%) of the rearrangement product as pale yellow crystals.

As the control, an identical mixture was refluxed for twenty hours (oil bath). Identical workup gave 861 mg (86%).

Example (40). 1-Phenyl-2-buten-1-ol (1.00 g, 6.75 mmol) was added to a solution of KOH (5.0 g) in an ethanol-water mixture (3:2, 25 mL). The mixture was heated at 100% power to 90 psi for ten minutes during which time the reaction temperature declined from 146°C to 144°C. After standard ethereal workup, the residue was chromatographed (hexanes-ether, 20:1 gradient to 1:1). The early fractions gave a mixture (215 mg) of 40a (11% of mass by 1H NMR , 24 mg, 2.4% net yield) and 40c (89% of mass by ^{1}H NMR, 191 mg, 16% net yield). From later fractions were obtained unreacted starting material (210 mg, 21%) and 40b (388 mg, 39%). All were colorless oils.

As the control, an identical reaction mixture was refluxed using an oil bath. After four days the mixture still contained predominantly starting material (TLC analysis). After workup the residue was subjected to ^{1}H NMR analysis. The crude oil (915 mg) contained 40b (7% of mass, 64 mg, 6% net yield), 40c (3% of mass, 27 mg, 2% net yield) and a negligible trace of 40a, with the balance unreacted starting material.

Example (41). Benzophenone (1.00 g, 5.50 mmol) and hydroxylamine hydrochloride (510 mg, 7.30 mmol) were added to a solution of triflic acid (2 drops) in 90% formic acid (5 mL). The mixture was heated at 35% power to 90 psi and was maintained for three minutes during which time the reaction temperature remained at 171°C. The cooled mixture was diluted with water and extracted with methylene chloride (3 x 30 mL). The organic phase was dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized (95% ethanol, 5% water) to give colorless crystals (1.07 g, 99%).

As the control, an identical mixture was refluxed for ninety minutes using an oil bath. Identical workup and recrystallization gave 1.04 g (96%).

Example (42). Sodium (460 mg, 20.00 mmol) was dissolved in absolute ethanol (20 mL) under nitrogen. This solution was transferred to a Teflon microwave vessel and *n*-butyldiethymalonate (4.32 g, 20.00 mmol) was added followed by urea (1.20 g, 20.00 mmol) dissolved in 22 mL of ethanol. The mixture was heated at 35% power to 90 psi. This pressure was maintained for six minutes during which time the reaction temperature was constant at 142°C. The cooled mixture was acidified to pH < 2 by the addition of concentrated HCl, concentrated to approximately 50% of the original volume and chilled in ice. The crystalline condensation product (293 mg, 80%) was filtered and washed with cold water.

An identical reaction mixture was refluxed for two hours using an oil bath after which a trace of starting material remained. Identical crystallization gave 2.31 g (63%) for this control experiment.

Example (43). Mesitylene (3.15 g, 26.20 mmol) and paraformaldehyde (375 mg which is equivalent to 12.50 mmol formaldehyde) were added to 90% formic acid (2.3 mL). The mixture was heated at 35% power to 26 psi. The temperature increased from 130°C to 142°C during a four-minute period. The mixture was permitted to cool to room temperature, then chilled in ice, and crystallization was initiated by seeding. The crystals (2.34 g, 75%) were washed with aqueous $NaHCO_3$ and then cold hexanes.

As the control, an identical mixture was refluxed for ninety minutes using an oil bath. Crystallization began spontaneously upon cooling to room temperature . The crystalline product (2.27 g, 72%) was filtered and washed as above.

Example (44). Freshly distilled phenylhydrazine (4.55 g, 4.21 mmol), cyclohexanone (5.21 g, 53.10 mmol) and glacial acetic acid (40 mL) were heated at 35% power to 46 psi and 175°C. These conditions were maintained for two minutes. The mixture was cooled, diluted with water and the resulting precipitate was filtered and washed with 75% ethanol. The tan powder (7.21g, 100%) was nearly pure by ^{1}H NMR analysis.

As the control, an identical mixture was refluxed for fifteen minutes (oil bath). Identical workup gave 7.19 g (100%).

Example (45). Magnesium turnings (479 mg, 19.70 mmol) and 25 mg of iodine were placed in a quartz vessel (Figure 1). The reaction vessel was capped and purged with dry nitrogen through one of the tubing fittings. Tetrahydrofurfuryl bromide (650 mg, 3.94 mmol) in 10 mL of anhydrous ether was added by syringe through the tubing fitting. The mixture was heated at 35% power to 90 psi for ten minutes during which time the reaction temperature dropped from 106° to 105°C. The cooled mixture was quenched with saturated aqueous NH_4Cl (1 mL) and benzene (20 µL) was added as an internal standard for GC analysis. The mixture contained 0.15 mmol / mL (38% yield) of the alcohol by GC analysis.

As the control experiment an identical mixture was refluxed for three hours using an oil bath. Identical quenching and analytical procedures indicated 0.17 mmol / mL (44% yield).

References

Abramovitch, R.A., 1991. Applications of microwave en-

ergy in organic chemistry. A review. Organic Preparations Procedures International 23: 683-711.

Abramovitch, R.A., 1992. Fischer cyclizations by microwave heating. Synletters 795.

Abu-Samra, A., Morris, J.S., Koirtyohann, S.R. 1975. Wet ashing of some biological samples in a microwave oven. Analytical Chemistry 47: 1475.

Bose, A.K., Manhas, M.S., Ghosh, M., Raju, V.S., Tabei, K., Urbanczyk, Lipowska, Z. 1990. Highly accelerated reactions in a microwave oven: synthesis of heterocycles. Heterocycles 30: 741.

Chapman, O.L., Engel, M.R., Springer, J.C., 1971. The total synthesis of carpanone. Journal of the American Chemical Society 93: 6696.

Davey, W. and Hearne, J.A. 1964. Chalcones and related compounds. Part IX. Preparation and rearrangement of some 1,3-diphenylprop-2-en-1-ols (chalcols). Journal of the Chemical Societ, 4978.

Gedye, R., Smith, F., Westaway, H., Baldisera, L., Laberge, L., Rousell, J. 1986. The use of microwave ovens for rapid organic synthesis. Tetrahedron Letters 27: 279.

Gedye, R.N., Smith, F.E., Westaway, K.C. 1988. The rapid synthesis of organic compounds in microwave ovens. Canadian Journal of Chemistry 66: 17-26.

Giguere, R.J., Bray, T.L., Duncan, S.M., Majetich, G. 1986. Application of commerical microwave ovens to organic synthesis. Tetrahedron Letters 27: 4925.

Giguere, R.J., Namen, A.M., Lopez, B.O., Arepally, A., Ramos, D.E., Majetich, G., Defauw, J. 1987. Studies on tandem ene/intramolecular Diels-Alder reactions. Tetrahedron Letters 28: 6553.

Harfenist, A., Bavley, A., Lazier, W.A. 1954. The oxidation of allyl and benzyl alcohols to the aldehyde. Journal of Organic Chemistry 19: 1608.

Iqbal, K. and Jackson, W.R. 1968. Addition reactions of conjugated double bonds. Part II. the occurance of 1,4- or 1,2-addition in the reduction of some aryl α,β-unsaturated ketones with metal hydride. Journal of the Chemical Society (C) 616.

Jassie, L. 1994. Hydrolysis of proteins, peptides and vitamin saponification. In: Microwave Enhanced Chemistry. (H. M. Kingston and S. J. Haswell, editors), American Chemical Society (in press).

Majetich, G. and Wheless, K. 1995. Microwave heating in organic chemistry: an update. In: Microwave Enhanced Chemistry. (H. M. Kingston and S. J. Haswell, editors), American Chemical Society (in press).

Mingos, D.M.P. and Baghurst, D.R. 1991. Applications of microwave dielectric heating effects to synthetic problems in chemistry. In: Chemical Society Review 20:1, 1-47.

Manhas, M.S., Bari, S.S., Raju, V.S., Ghosh, M., Bose, A.K. 1991. Abstracts of Papers, Fourth Chemical Congress of North America, New York, N.Y.; American Chemical Society, Washington, D.C. ORGN-195.

Ramachandran, S. and Newman, M.S. 1973. 1,6-Dioxo-8a-methyl-1,2,3,4,6, 7,8,8a-octahydronaphthalene. Organic Syntheses, Collective Volume 5, 486.

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